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Novel Approaches in Obesity, Metabolism, and the Immune System: Mechanisms, Therapeutics, and Future Directions

Lingyun Xia and Dani Qin*

Department of Pediatrics, The Affiliated Yixing Hospital of Jiangsu University, Wuxi, China

Abstract

The obesity pandemic all over the world has remarkably raised the rates of metabolic disorders and complications, as well as immune features. This review analyses the interplay of obesity, metabolism, and the immune system, along with the emerging alternative methods of study and treatment of the disease. We review the emerging evidence on the role of adipose tissue inflammation, gut microbiota and new therapeutic implications in the immuno-metabolic field. By drawing on the knowledge of different studies, we will give an overview of the existing state and future areas of work on the problem of obesity and its related health problems.

Keywords: Obesity; Metabolism; Immune system; Adipose tissue

Introduction

Growing obesity epidemic

Obesity has been an epidemic worldwide, affecting hundreds of millions of people, and it is a major health concern to society [1]. According to the estimation issued by the World Health Organization (WHO), the number of overweight adults exceeds 1.9 billion, and at least 650 million of them are obese [2]. This enormous rise correlates to a high increase in the incidence of metabolic diseases, such as Type 2 Diabetes Mellitus (T2DM), heart illnesses, and alcoholic fatty liver disease [3]. Obesity causes not only a personal financial toll, but also a societal one, as it impacts the health care costs and the loss due to productivity loss.

Link between obesity and immune dysfunction

Obesity is no longer a cosmetic problem but rather is a complex metabolic syndrome with a low-grade inflammatory state. Adipose tissue used to be regarded as a passive energy storage organ, but it has now also been discovered to be an active endocrine and immune organ [4]. This tissue changes drastically in obese people; changes include hypertrophy, hypoxia, and infiltration of immune cells. The changes lead to the synthesis and secretion of a large number of inflammatory cytokines Tumor Necrosis Factor-alpha (TNF-a), Interleukin [IL]-6, IL-1b, adipokines (Leptin, Adiponectin, Resistin and Visfatin), and chemokines (CCL2, CCL5, and CXCL10) contributing to systemic inflammation and metabolic disorders [5].

Need for novel approaches

Conventional weight-loss interventions, such as diet, workouts, and bariatric surgery, have yielded mixed results. They are, however, limited by patient compliance, surgical risks and long-term sustainability. A demand exists to develop innovative treatment methods that alleviate the immunometabolic processes related to obesity and obesity-related complications. Discoveries about the complicated interactions between obesity, metabolism, and the immune system have provided new directions in creating specific cures.

Literature Review

Immunometabolic crosstalk in obesity

Adipose tissue inflammation: Adipose Tissue Macrophages (ATMs) are important in triggering and perpetuating inflammation in obese subjects [6]. These macrophages are pro-inflammatory M_1 type that synthesizes cytokines, among others TNF-α, IL-6, and IL-1b [5,7]. The cytokines not only stimulate local inflammation but also predispose to insulin resistance within the adipose tissue and other metabolic organs. Most recent findings show that ATM polarization to anti-inflammatory M_2 can enhance insulin sensitivity and functional metabolism [8]. Figure 1 illustrates the inflammatory response within obese adipose tissue, emphasizing the roles of M_1 and M_2 macrophages, Th_2 cells, T cells, Natural Killer (NK) cells, and B cells. The transition from an anti-inflammatory to a pro-inflammatory immune cell profile contributes to sustained inflammation and metabolic dysfunction associated with obesity.

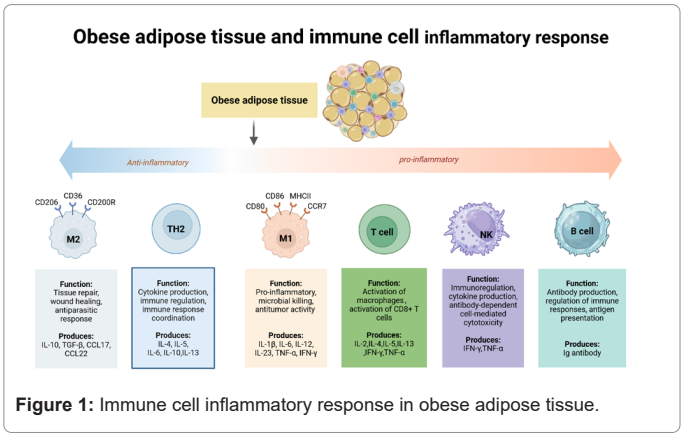

Figure 1: Immune cell inflammatory response in obese adipose tissue.

Obesity shifts the state of adipose tissues from an anti-inflammatory to a pro-inflammatory. The key anti-inflammatory cells and their functions are:

- M_2 macrophages: Repair tissue and produce IL-10

***Corresponding author:** Dani Qin, Department of Pediatrics, The Affiliated Yixing Hospital of Jiangsu University, Wuxi, China, E-mail: staff1587@yxph.com

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- Th_2 cells: Regulate immunity and produce IL-4 pro-inflammatory
- M_1 macrophages: Drive inflammation, produce IL-1β, TNF-α
- T cells: Activate immune cells and produce IL-2 and interferon-gamma (IFN-γ)
- NK cells: Mediate cytotoxicity and secrete IFN-γ
- B cells: Produce antibodies

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Immune cell interactions: The complex interplay between immune cells significantly shapes the inflammatory milieu within adipose tissue. Macrophages play a crucial role in obesity-induced inflammation. They produce pro-inflammatory cytokines, including TNF-α, which not only increase the local inflammatory response but also act as chemoattractants [5]. These cytokines recruit various other pro-inflammatory immune cells, including CD4+ T cells, NK cells, and innate lymphoid cells, into the adipose tissue [9]. Upon infiltration of these immune cells, the immune response is further enhanced, resulting in a self-sustaining process of inflammatory responses.

Homeostasis of the various populations of immune cells is very tenuous and a main determinant of the overall inflammatory status and metabolic health.

The differentiation of a pro-inflammatory profile (an increase in the proportion of M_1-macrophage type, Th1, and cytotoxic T cells, and a decrease in anti-inflammatory cells, such as M_2-macrophage type, regulatory T cells, and invariant NK T cells) leads to worsening of the metabolic environment [10]. This disproportion is closely linked to insulin resistance and other metabolic disorders related to obesity.

Gut microbiota and the immune-metabolic axis

Gut microbiota composition in obesity: Gut microbiota is a complex ecosystem of microorganisms in the gastrointestinal tract. It is very significant in host immunity and metabolism [11]. It has been shown that obese patients commonly show varying gut microbiota composition, which is low in diversity and enriched in firmicutes to bacteroidetes ratios [11]. Low-grade inflammation and diet-derived energy overharvest are connected to this dysbiosis [12]. In turn, the regulation of the gut microbiome can be a promising avenue for treating obesity.

Mechanisms of gut microbiota-immune crosstalk: The homeostasis of the gut is vital and is highly dependent on the orchestration between the innate and adaptive immune systems of the host and the microbial complex of the intestines. Depending on the interaction with the host immune system, the microbiome can produce Short-Chain Fatty Acids (SCFAs) [13], Lipopolysaccharides (LPS), and other metabolites [14]. Anti-inflammatory SCFA can include acetate, propionate, and butyrate which can affect immune cell functioning and metabolism [13]. On the other hand, LPS signaling via toll-like receptor 4 can initiate inflammation [15]. Learning about these mechanisms is vital in laying down therapeutic measures to treat diseases related to gut dysbiosis and immune deficiency, such as obesity, inflammatory bowel disease, and metabolic disorders.

Novel therapeutic approaches

Immunotherapies: Immunotherapy has tremendously progressed in the recent past, showing the potential of affecting immune response in the context of obesity and metabolic disorders. Biologic anti-inflammatory treatments, which are specific, like anti-TNF-alpha (anti-TNF-alpha) and anti-IL-1beta, have proven to be rather effective in pre-clinical trials. They are potential therapeutic agents that could lower levels of inflammation and increase insulin sensitivity.

Inhibition of immune checkpoints, which became widely used in the treatment of cancer, is also attracting interest. There is active research on their ability to regulate immune cell activity in the context of obesity. Such a discovery can lead to new treatment measures, which could transform the mitigation of obesity and the co-existing metabolic disorders.

Metabolic modulators: Obesity is a multifactorial metabolic disease that causes metabolic disturbance and affects other physiological systems. The metabolic modulators have also shown potential in the treatment of obesity and related metabolic problems. Despite their development in treating T2DM, GLP-1 agonists and SGLT2 inhibitors reduced cardiovascular incidence and resulted in weight loss [16].

Tirzepatide is a new drug candidate of potential use in the management of metabolic disorders related to obesity and T2DM. It works by aiming at the ATM activity and reducing inflammation linked to obesity [17]. Besides improving metabolic performance, tirzepatide also has an anti-inflammatory effect. The two-fold action also illustrates the close symbiosis between metabolism and immune stimulation as a new potential approach to the treatment of obesity.

Microbiome-based interventions: The emerging field of microbiome research has found microbiome-based interventions very promising as a means of correcting the imbalance in the microbiota and improving metabolic health. Fecal microbiota transplantation, probiotics, and prebiotics are becoming novelties as a replenishment of gut microbiota to enhance metabolic fitness [18]. Clinical trials have also shown that certain probiotic strains may suppress inflammation and also enhance insulin resistance among the obese [19]. These results indicate the possibility of microbiome interventions as an effective way of restoring gut microbiota homeostasis and metabolic health. These interventions are likely to be used as new and viable methods of addressing metabolic disorders and improving well-being as research in this field progresses.

Gene editing and personalized medicine: The research on the human genome has taken new dimensions in the last decade with revolutionary developments in genome editing technologies. These technologies have provided scientists with the instrument to study deeper into the functions of single genes and their effects on a multiplicity of diseases. Current gene-editing technology, like CRISPR-Cas9, is used to edit obesity-linked genes and their regulating components [20]. The customization of medicine that is coming is being developed to individualize therapy towards the patient with genetic, microbiome, and immune profiling.

Integration of therapeutic strategies: The above treatment methods indicate the complexity of obesity therapy. Figure 2 gives an overview of existing and new therapeutic methods of obesity treatment, including lifestyle choices, medicines, surgery, immunotherapy, microbiome-based treatment, and gene editing. This integration brings to the fore the need for a personalized and multi-targeted approach in the mitigation of obesity and its complications.

Presently, obesity treatments fall under four major categories as outlined below. Lifestyle interventions: Dietary changes, physical activity, and psychological support, such as cognitive behavioral therapy, behavioral therapies, especially microbiota transplantation. Pharmacological Treatments: Orlistat is orally taken, and GLP-1 receptor agonists are injectable. Surgical Options: These include the Roux-en-Y gastric bypass, the sleeve gastrectomy, and adjustable gastric banding. New treatments: Immunomedicine (colonies and immune gates) as well as genetic-based medicine (CRISPR/CAS9 and antisense oligonucleotide therapies). Therapy for obesity must be individualized, and the combination of several methods must become the way of overcoming the problem. Created with Biorender.com.

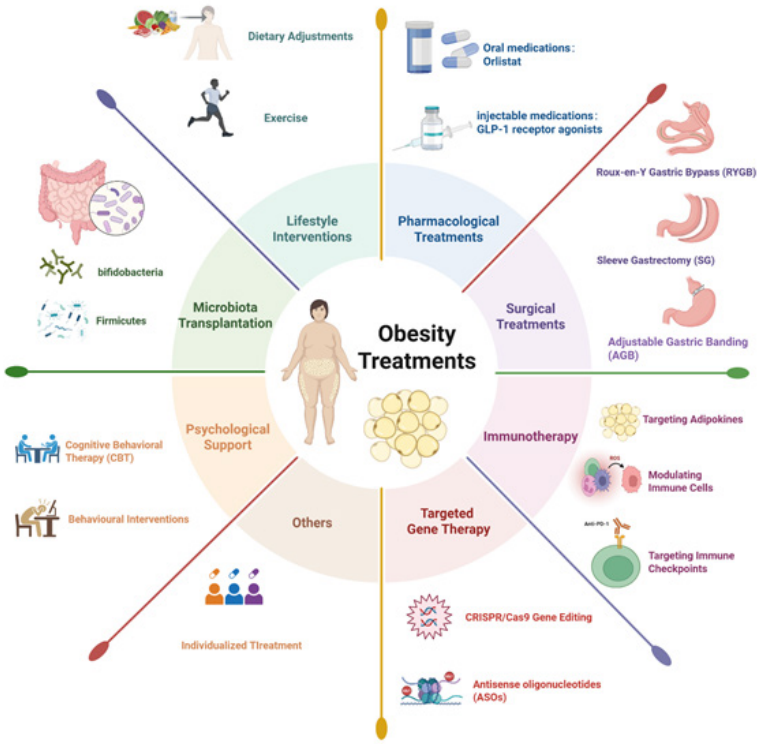

Figure 2: Multidisciplinary approaches to obesity treatment.

Discussion

Clinical implications of novel therapies

Development of new treatments addressing immunometabolic pathways is a potential solution for the treatment of obesity. They can create a weight-loss efficacy, metabolic complications (high insulin resistance and inflammation), and a wide range of personal care alternatives.

Nevertheless, there are barriers to the use of these therapies in clinical practice. The obese population is heterogeneous due to genetics and lifestyle, which makes it hard to predict the response to treatment of an individual. In addition, the complicated immunometabolic network suggests that the slight modifications have general implications. It is, however, difficult to predict how these therapies will act on different patients.

The long-term safety and efficacy data are important in the overall effectiveness of the treatment. Although initial trial results are promising, limited data hamper a thorough evaluation of these therapies. Collecting field-based evidence through post-market surveillance and registries is vital for understanding their long-term impacts.

Future research directions

Future research should focus on identifying biomarkers that can predict treatment response and guide personalized therapy. Integrating multi-omics approaches (genomics, transcriptomics, proteomics, metabolomics) will provide a more comprehensive understanding of the immunometabolic mechanisms underlying obesity and enable the development of targeted interventions. Additionally, interdisciplinary collaboration between immunologists, endocrinologists, microbiologists, and clinicians is essential to accelerate the translation of novel findings into effective clinical therapies.

Conclusion

The interplay between obesity, metabolism, and the immune system is a complex and dynamic field of research with significant clinical implications. Novel approaches that target the immunometabolic axis offer exciting opportunities for developing more effective therapies for obesity and its associated health issues. As our understanding of these mechanisms continues to evolve, so too will the potential for personalized and precision medicine in the treatment of obesity and metabolic disorders.

Author Contributions

Dani Qin and Lingyun Xia collaboratively developed the conceptual framework of the study. Lingyun Xia was responsible for drafting the initial manuscript, while Dani Qin managed the creation of visual materials. They have thoroughly reviewed and consented to the submission of the final manuscript for publication.

Conflicts of Interest

The authors declare no conflict of interest.

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